How can nanotechnology help the fight against breast cancer?

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Abstract

In this Review we provide a broad overview on the use of nanotechnology for the fight against breast cancer (BC). Nowadays, detection, diagnosis, treatment, and prevention may be possible thanks to the application of nanotechnology to the clinical practice. Taking into consideration the different forms of BC and the disease status, nanomaterials can be designed to reach the most forefront objectives of modern therapy and diagnosis. We here analyzed in details three main groups of nanomaterial applications for BC treatment and diagnosis. We have identified several types of drugs successfully conjugated with nanomaterials. We have analyzed the main important imaging techniques and all nanomaterials used to help non-invasive, early detection of the lesions. Moreover, we have examined theranostic nanomaterials as unique tools, combining imaging, detection, and therapy for BC. This state of the art provides a useful guide depicting how nanotechnology can be used to overcome current barriers in BC clinical practice, and how it will shape the future scenario of treatments, prevention, and diagnosis, revolutionizing the current approaches, i.e., reducing suffering related to chemotherapy.

1. Introduction

Breast cancer represents a malignant tumor where breast cells grow out of control and overcrowd normal cells. BC represents the most common type of cancer affecting women worldwide, and it is the second leading cause of death in the United States with 253 000 new cases estimated in 2017.[1] When BC occurs, it is crucial, for the prognosis, to get early detection, followed by opportune treatments including surgery and chemotherapy. Nowadays, the most important clinical analyses comprise mammogram, ultrasound exams, and nuclear magnetic resonance imaging (MRI). Moreover, biopsy and blood chemistry studies help for a more accurate diagnosis of BC. Around 4.9 million breast biopsies are performed every year in the world, and 3.2 million of them are checked for screen detection of non-palpable breast lesions, of which a third is found to be malignant.[2]

However, by considering the current methods of BC diagnosis, any doctor can ensure a survival rate close to 100%. On the other hand, if we focus on BC therapy, many current treatments are invasive, involving several breast biopsies, wire-guided localization, and eventually surgical removal. All current treatments including chemotherapy and prophylactic strategies are disfiguring, invasive, and associated with significant side effects.[3]

For all these reasons new diagnosis strategies and new effective and less toxic therapies are urgently needed. The recent advances in technology and engineering have led to the application of nanotechnology in medicine with the development of new nanoscale biomedical systems.[4] Nanomaterials have been explored for biomedical research because of their extraordinary physicochemical characteristics. In particular, cancer nanotechnology has proposed excellent approaches to cancer detection, diagnosis, and treatment with limited toxicity compared to the traditional cancer therapy.[5] In this context, nanotechnology can create human-made materials in the nanoscale range, the same scale where cellular and biological processes take place.[6] The major potential of cancer nanotechnology includes the possibility to engineer nanovehicles with multiple molecules that, because of their small size, can penetrate tumors with high specificity, consequently with significantly fewer side effects.[7-9] Furthermore, techniques for nonsurgical ablation of tumors have been developed, leading to the complete destruction of tumor cells by the direct application of thermal and chemical therapies using nanomaterials, composed of metals, lipids, or polymers.[10] Therefore, cancer nanotechnology brings in the scenario of BC oncology huge expectations, and nanomaterials can be adapted the different BC forms and disease status. Because of the high degree of control, the characteristics of human-made nanotools can ensure new perspectives. Nanomaterials in BC can act as: i) drug nanocarriers, ii) nanodiagnostic tools, and iii) theranostic tools.

Regarding drug delivery, nanomaterials can be designed to transport chemotherapeutic drugs directly to the breast cells using specific antibodies to target the cancer site.[11] Doxorubicin (Dox) linked to nanomaterials is the most investigated drug for cancer therapy. Very recently the group of Ferrari has described an injectable nanoparticle generator (iNPG), consisting of a discoidal micrometer-sized particle that can be loaded with Dox conjugated to poly(L-glutamic acid) (pDox).[12] Intravenously injected iNPG-pDox accumulates into the tumor region and shows enhanced efficacy in mouse models of metastatic BC.

In the context of the development of diagnostic tools, there are many successful examples of nanomaterials applied to visualize BC [i.e. superparamagnetic iron oxide nanoparticles (SPIONs) and magnetic nanoparticles (MNPs)]. Different studies have reported a sensitivity of 73-100% and a specificity of 92-98% in the lymph node using SPIONs.[13] Among other advantages, SPIONs are useful for the early detection by MRI, displaying also a good immune-compatibility and echogenic properties.[14] Today other nanotechnology-enabled systems are in clinical trials. For example, a [^{18}F]-FAC isodeoxycytidine analogue for deoxycytidine kinase (DCK) labeled with fluorine ^{18}F, was proposed as a novel PET imaging probe.[15] Nanoparticle MRI contrast agents that bind the αvβ3-intregrin, expressed on the surface of the newly developing blood vessels associated with early tumor development, were developed.[16] Lymphotrophic superparamagnetic nanoparticles developed by the MIT-Harvard Center for Cancer Nanotechnology Excellence were used to identify small, otherwise undetectable, lymph node metastases.[16]

Before initiation of a cancer treatment, it is essential to carry out diagnostic imaging procedures to understand the type of cancer lesion. In this context, theranostic agents can combine diagnostic and therapeutic strategies into one procedure.[17] Hosoya H. *et al.*[18] described a hydrogel-based nanoplatform conjugated with Dox that enables ligand-directed tumor targeting and multimodal imaging. The data obtained using this strategy suggest that targeted hydrogel photothermal therapy represents a functional theranostic application such as image-guided approaches for diagnostic and therapeutic monitoring. Another revolutionary nanomaterial, graphene, and in particular graphene oxide (GO), has been studied for medical applications including tissue engineering, drug delivery, and gene transfection; many studies have explained its potential as molecularly-targeted and dual-modality imaging agent for *in vivo* imaging of BC.[19]

In this Review, our purpose is to point out what are the most promising nanomaterials that can perform a breakthrough revolution in the scenario of BC. We provide a thorough overview of nanomaterials that have been so far investigated for the fight against BC, analyzing the most interesting publications present in the literature. We analyze the applications on drug delivery, imaging, and theranostics. We discuss all specific potentialities of the nanotechnology tools to overcome current barriers, to reduce toxicity, and to avoid suffering from anticancer treatments. This review aims to shed light on the challenges and hope offered by the different nanomaterials in the fight against BC. We propose a comprehensive analysis of the nanomaterials enrolled in this oncology context.

2. Overview and studies selection criteria

Initially, we have analyzed in details three main nanomaterial applications for BC: i) drug delivery, ii) imaging, and iii) theranostics.

For this analysis, we performed a PubMed search using the following keywords: breast cancer, nanotechnology, nanomedicine, nanoparticles, nanomaterials, drug delivery, theranostics, and imaging. Keyword searching was also performed in different combinations. High impact review articles served as additional tools. The list of reported studies includes all retrieved publications from 2009 to December 2017. In Table S1, S2 and S3 we show a full and deep characterization of all applications based ontype of materials, conjugated drugs, imaging modialities, applications other than imaging, model, type of species examined (human, mouse and their combination), other types of cancer other than BC.

Figure 1 represents the number of publications over the years, the types of applications on therapy and diagnosis and the types of species examined in the cited works. The trend, from 2009 to December

2017, indicates an oscillating tendency in the studies on BC (Fig. 1A); i.e., the number of retrieved publications in 2011 was 1.5 higher compared to 2009. After a clear decrease in 2012, the state of publications in all the following years was higher than 2009. Imaging is the first application (58%), while 35% of the articles are referred to theranostic applications combined with drug delivery (Fig. 1B). Besides, drug delivery, a single application, is reported in 7% of the works. In Fig. 1C we show the relative percentage of publications describing human cell lines (*in vitro* and *ex vivo)*, mice (in *vivo, vitro,* and *ex vivo*), or both. Although there are no many differences regarding the percentage of publications of the examined species, we found that the majority of the studies has been carried out in humans cells (39%), 28% in mice, and 33% in both of them. International variations in BC incidence rates reflect differences in the availability of early detection tools as well as risk factors.[20] In this context, we analyzed the countries where BC studies were carried out, taking into consideration the affiliation of the corresponding author (Fig. S1). We found that the majority of the studies (39%) were conducted in USA, 26% in China, 5% in South Korea, 4% in Japan, Singapore and India, 3% in UK, 2% in Canada, Italy, Iran and Australia; a very few studies were conducted in other countries (< 2%). By the analysis of these percentages, we could conclude that there is no correlation between countries and incidence of BC. In fact, considering countries like United States where there is a high number of scientists, it is obvious to expect a larger amount of published works. A careful analysis of these data showed that there is not a strong correlation between the number of studies published and the relative incidence of BC. More developed countries represent about one-half of all BC cases with 38% of mortality. In fact, as reported in the pie graph (Fig. S1), USA, China, South Korea has got the highest percentage of studies compared to the other countries, but it was estimated that the higher mortality from BC occurs in Asian countries, as Qatar, India, and Iran.

Since BC may lead to metastasis in other regions of human body, many scientists focused at the same time on other cancer forms together with BC. We found that many authors studied BC specific ligand/cell surface also identified in other type of cancers, or BC overexpressed receptors using other cancers as negative controls. Therefore, we report other types of cancer investigated with BC (Fig.

2). Lung cancer were studied in 22% of the papers, pancreatic and prostatic cancer in 19% of the papers, ovarian in 13%. Melanoma, colon and liver cancers were studied in 6% of the publications and the other types of cancer including gastric, glioblastoma and bone cancer resulted in3% of the cases (Fig. 2).

3. Drug Delivery

Drug delivery is a key nanotechnology application. In Table S1 we illustrate all publications on drug delivery in the context of BC. However, this type of application alone is reported in only the 7% of the cases considered. Indeed, in many examples, drug delivery applications refer to theranostic applications (corresponding to 35% of the studies). Analyzing the different publications, we found several types of drugs used in drug delivery or in combination leading to theranostic nanomaterials (Fig. 3). These drugs comprise Dox, herceptin, paclitaxel (PTX), dextran, curcumin, mitoxantrone, tamoxifen, methotrexate, pentoxifylline, and docetaxel**.** Dox represents the most important anticancer chemotherapeutic drug.[21] Indeed, its ability to intercalate DNA bases, inhibiting the topoisomerase II enzyme during DNA transcription was widely demonstrated.[22] Many studies used nanomaterials conjugated with Dox as an innovative cancer therapy.[22-27] Herceptin was used for the treatment of metastatic BC, thanks to its properties of blocking cells proliferation.[28-33] Recently, Wang *et al.*[34] reported a synthesis of a particular multifunctional anti-cancer complex based on functionalized magnetic nanoparticles (MNPs) and quantum dots (QDs) with a dual-drug combination. In detail, the PTX/MNPs/QDs@Biotin–PEG–PCDA nanoparticles nanoparticles have shown a high uptake by BC cells (MCF-7/ADR) and good drug release. These nanoparticles are able to combine various proprieties useful for imaging (QDs), targeted delivery and uptake (MNPs), and dual drug treatment using two drugs (i.e., PTX and curcumin). Curcumin, a natural compound extracted from *curcuma longa*, helped to obtain a high PTX accumulation in the tumor target and induces a down-regulation of drug efflux transporters. Moreover, PTX has shown excellent efficacy in a wide spectrum of cancer treatments, but its formulation has led to serious side effects in patients, as neurotoxicity, nephrotoxicity and allergic reaction. Modified PTX as nanomicelles was developed to overcome these obstacles and multidrug resistance.[35]

Zhao et al.[36] described hybrid paclitaxel nanocrystals that integrated fluorescent molecules for therapeutic and imaging in a breast tumor. The authors observed a more efficient anticancer effect of this system in mice with breast tumor than in mice treated with pure PTX. The hybrid PTX nanocrystals have shown the ability to easily accumulate in the tumor area following intravenous administration. Others described PTX release directly into the tumor sites for theranostic nanomedicine application [34-37] and drug delivery.[38] In the third position of the most important drugs used in the cancer fight, we found curcumin, a compound endowed of interesting properties including an anti-inflammatory action.[39] Curcumin can specifically modulate the expression of proteins in proliferating cells, in adhesion and in migration, and it is used as an anticancer drug to prevent metastatic formation or to limit cancer progression.[40,41]

Furthermore, other types of drugs such as dextran[33, 42, 43] or docetaxel[44, 45] were loaded into nanoparticles for cancer detection, while mitoxantrone,[46] tamoxifen,[47] methotrexate,[48] pentoxifylline,[49] docetaxel,[50, 51] cisplatin and gemcitabine were combined for the development of theranostics materials.[52] Recently, the group of Chan provided quantification of the delivery efficiency of nanoparticles at the tumor site. They reported a bombshell work whose meta-analysis suggested that very few "targeted" nanoparticles reach the target. According to this analysis, only 7 out of 1000 engineered nanoparticles are able to accumulate into the tumor *in vivo*.[53]

4. Imaging

Nowadays, nanotechnology based on imaging represents a very promising solution for non-invasive investigations of cancer lesions. We found that in 58% of the examined studies the first approach against BC is based on the use of nanotools for imaging (Fig. 1B). Breast imaging can be undertaken using MRI, the most commonly available modality, thanks to its rapidity and high resolution (Fig. 4A).[54] Different nanoparticles with appropriate surface modification have been used *in vivo* as MRI contrast agents because of their high magnetization and nano-size.[55] In particular, the surface coating was exploited to create non-toxic and biocompatible nanomaterials (see Table S2).[56-78] For example, Medarova *et al*.[79] have modified SPIONs with Cy5.5 dye and conjugated them to specific peptides. This tumor-specific contrast agent was able to successfully target the under-glycosylated MUC-1 (uMUC-1) tumor antigen, present in over 90% cases of BCs.

MRI is followed by two other techniques, namely fluorescence imaging (FI)[5, 64, 78, 80-119] and confocal laser scanning microscopy (CLSM) (Fig. 4A).[58, 64, 67, 73-75, 120-134] Both of them have shown to be excellent imaging tools for many *in vitro* studies on murine and human cancer cells.

Pan *et al*.[120] described *in vitro* cancer detection of human cells (MCF-7) using fluorescent quantum dots (QDs) as luminescent probes for targeted imaging. The authors described a new strategy to prepare QDs formulated in folate-decorated nanoparticles (PLA-TPGS/TPGS-COOH) (PLA-TPGS, poly(lactide)-D-α-tocopheryl polyethylene glycol succinate) for BC detection and diagnosis at its early stage. They demonstrated that functionalization with a copolymer was able to improve imaging sensitivity with reduced side effects on normal cells. Another imaging technique used in BC studies is the near-infrared (NIR) optical imaging, [56, 79, 83, 96, 97, 99, 107, 112, 127, 132, 135-143] which represents the fourth most exploited type of modality in the total of the examined studies. Through NIR fluorescence images, the authors analyzed directly *in vivo* the biodistribution of many nanomaterials in different organs and their elimination. Bardhan *et al*.[56] used modified gold nanoshells (AuNSs) with fluorophores to enhance the fluorescence in live mice grafted with human cancer cell lines over 72 h. The nanocomplex, conjugated with specific antibodies to target human epidermal growth factor receptor 2 (HER2) overexpressed in BC, provided significant information regarding the distribution of nanomaterial, and represents a new approach for cancer therapy and non-invasive treatment for soft-tissue tumors.[56]

Moreover, we found that computed tomography (CT)[70, 113, 139, 144-152] is at the fifth position in terms of number of works related to BC, while other techniques are less used, including superconducting quantum interference device (SQUID),[94, 153] surface enhanced Raman scattering (SERS),[81, 154-159] synchrotron X-ray micro-imaging (X-ray),[150, 152, 160, 161] positron emission tomography (PET),[106, 115, 142, 162] and fluorescence molecular tomography (FMT).[70, 73] We reported that single-photon emission computed tomography (SPECT),[163] ultrasound imaging (US),[71] intermolecular quantum coherence (iMQC),[164] optical coherence tomography (OCT),[165] ultrashort echo time (UTE)[166] are in the last positions as imaging techniques used (Fig. 4A). Focusing on the imaging tools, we found that the first most studied nanomaterials are SPIONs (Fig. 4B).

Many publications have shown the interesting potential of SPIONs for tumor detection, cancer therapy and drug delivery.[13, 54, 57, 59, 61, 64, 67, 68, 74-79, 94, 100, 104, 145, 148, 164, 166-170] SPIONs are applied as molecular imaging probes due to their monodisperse size distribution, but for biomedical applications, a surface modification [i.e., with poly(2-hydroxyethyl aspartamide)] is necessary to make them stable under physiological conditions and to avoid the uptake by phagocytic cells.[57] A recent publication has shown their use for gene therapy. Lin *et al*.[74] discovered that SPIONs conjugated with small interfering RNA (siRNA) were able to silence the target messenger RNA, consequently reducing the expression of P-glycoprotein (P-gp), a cell membrane protein responsible of multidrug resistance. Through this gene therapy, the authors demonstrated an excellent down-regulation of P-gp in MCF-7/ADR human BC cell lines in orthotopic mouse model.

In the same way of SPIONs, other small size (5-8 nm) magnetic nanoparticles (MNPs) have also shown the same characteristics in terms of,[58, 69, 70, 72, 73, 83, 102, 125, 126, 131, 134, 139, 153, 171] biodistribution, and ability to carry more compounds thanks to their high surface availability. In this context, Yigit *et al.*[171] used MNPs linked to microRNA (miRNA) for gene therapy. The treatment of human BC cells (MDA-MB-231) *in vitro* and *in vivo* with the nanocomplex down-regulated a pro-metastatic microRNA (miR-10b) arresting the metastatic process, thus preventing the formation of lymph node metastases. Regarding QDs, we found that they are in the third position as nanomaterials for imaging. Thanks to their fluorescence properties upon excitation, their high brightness and photostability, they represent unique nanomaterials ideal for *in vivo* imaging in animal cancer models, as shown in the measurement of the receptor expression level of type I insulin-like growth factor receptor (IGFIR) involved in BC proliferation and metastasis.[122] QDs have been coated with polymer to enhance biocompatibility,[64, 89, 92, 95, 101, 114, 120, 133, 172] or conjugated with antibodies to detect overexpressed receptors.[85, 88, 90, 91, 98, 99, 107-110, 116, 122, 135]

The fourth position is held by gold nanoparticles, used for tumor detection, diagnosis, and cancer therapy, due to the possibility of an easy surface modification.[173] The advantages of these nanomaterials include non-cytotoxicity, chemical stability, and high affinities for biomolecules.[121] Indeed, they can scatter visible and near-infrared light through surface plasmon resonance, so that they have been used in many microscopic techniques including CLSM,[121, 130, 174] CT,[113, 147, 149, 150, 152] FI,[5, 87, 103, 113] and other imaging techniques like X-ray,[150, 152, 160] NIR imaging[141] and SERS.[155, 175] Finally, other imaging nanomaterials (Fig. 4B) such as poly(lactic-co-glycolic) acid nanoparticles (PLGA),[71, 80, 97, 176] mesoporous silica nanoparticles (MSNs),[75, 86, 140, 142] liposomes,[93, 100, 144, 146, 177, 178] silica- AuNSs,[56, 137, 154, 165] gold nanorods (GNRs),[78, 84] carbon nanotubes (CNTs),[82, 129] nanoglobules [62, 66], graphene oxide,[115, 163] and nanodiamonds (NDs)[179] have been studied for breast tissue imaging and cancer therapy (see Table S2).

5. Theranostics

Recently, nanotechnology has provided new strategies that combine therapy and diagnosis approaches. The introduction of the word "*theranostics*" represents a well-established field of nanotechnology where multifunctional materials can be used for the detection and treatment of cancer disease in a single procedure. Of particular importance is the simultaneous combination of contrast agents and therapeutic functions using chemically-modified nanoparticles or fluorescent probes.[180, 181] In Table S3 we report a characterisation of all theranostic applications found in the literature for BC. Regarding nanoparticles, we found MNPs in the first position in terms of theranostic materials investigated, followed by calcium phosphosilicate composite nanoparticles (CPSNPs), liposomes, AuNPs and GNRs, AuNSs, CNTs and polymers (Fig. 5). Theranostic MNPs have demonstrated excellent performances in tumor detection,[182-185] drug delivery,[184, 185] and cancer therapy in mice model studies.[186, 187] Part of the works examined were carried out *in vitro* on MDA-MB-231,[40, 41] MCF-7,[41, 47, 188, 189] H1299 human cell lines,[188] as preliminary studies to evaluate the response to cancer therapy. Basuki *et al.*[188] described the theranostic application of MNPs loaded with polymers and Dox in *in vitro* experiments using MCF-7 on H1299 human cell lines. The authors demonstrated accumulation of MNP-Dox in lung and BC cell lines through MRI and Dox release to cancer cells using CLSM and FI techniques. For theranostic, GNPs, AuNSs have raised interest in photodynamic therapy,[190, 191] photothermal therapy,[180, 192-194] ultrasonography[192] and gene therapy.[180] On the other hand, in the context of imaging, AuNPs have shown main applications regarding tumor detection.[18, 29, 195-200]

In the third position we found other known theranostic materials such as MSNs used for tumor targeting and drug delivery,[30, 201-203] GNRs for tumor detection and drug delivery,[31, 32, 204] gene therapy,[205] and photothermal therapy.[206, 207] We also found liposomes for tumor detection and drug delivery,[46, 50, 208, 209] and other new theranostics systems like CNTs[48, 210-213] and CPSNPs.[214, 215] In particular, we have shown that CNTs have good echogenic properties like contrast agents, with a promising future in the field of theranostic applications.[216] Even though positioned in the fourth position, QDs have acquired more importance in the field of theranostic applications. Rizvi *et al*.[217] reported an *in vitro* experiment using QDs loaded with antibodies for HER-2 localization in fixed and live cells (SK-BR-3 and MCF-7 cells). This study underlines how QDs coated with mercaptoundecanoic acid appeared non-toxic up to 24 h of exposure, and an excellent *in vitro* imaging agent. For this reason, QDs can be potentially used for targeted therapy in image-guided surgery and cancer therapy to directly destroy tumor cells. In addition to traditional nanomaterials, the combination of polymeric materials has opened a new way for theranostic nanomaterials, known as nano-complexes (Fig. 5). Their properties have allowed a controlled release of drugs in addition to many medical applications, like photoacoustic tomography,[218] photothermal therapy,[219-221] photodynamic therapy,[222] drug delivery[37, 49, 223-229] and cancer therapy.[230-234]

During the last years, graphene-based materials have been investigated in biomedical applications thanks to its unique intrinsic chemical and physical properties.[235] Excellent electrical conductivity, ideal photothermal response, large surface area, and versatile chemistry have stimulated the researchers to explore graphene based materials for applications in tissue engineering, drug delivery, molecular imaging and others. For example, Shi *et al*.[236] reported reduced GO (rGO) as an excellent photothermal agent that enabled *in vivo* tumor ablation. rGO could be also used as theranostic materials to integrate imaging and therapeutic components to fight cancer.[236] Recent researches of nanotechnology based on other carbon nanomaterials as NDs, CNTs, and fullerenes have provided good results about their possibility to become theranostic agents in the different field of nanomedicine such as drug delivery, regenerative medicine, bioimaging. Carbon nano-onions (CNOs) showed the same vectorization characteristics possessed by CNTs, as we described in a previous work.[237] Recently Bartelmess *et al*.[238] demonstrated a simple cell-penetration capability of CNOs in an *in vitro* MCF-7 human BC cell line. Boron dipyrromethene (BODIPY) functionalized CNOs exhibited high fluorescence intensity for high-resolution imaging and did not show significant toxicity effects. These results make modified CNOs as new theranostic materials able to combine imaging, targeting and therapeutic modalities.

6. Conclusions and future views

We here reported a thorough and detailed review on nanoscale innovations against BC proposed in the last nine years. We have evidenced an increasing interest in the study of nanotechnological applications to BC. Nanotechnology offers a possibility for early breast lesion detection and search for more efficient therapies to significantly impact the degree of mortality of BC patients. Despite numerous studies on the application of nanotechnology in medicine, the hypothetical benefits still need to be clarified. Most of the nanomaterials tested have not been able to provide high efficiency for clinical use. Considering the intrinsic physicochemical properties of nanomaterials and all works analyzed here, superparamagnetic iron oxide nanoparticles, quantum dots, graphene and liposomes represent the best choice as advanced drug carriers for BC therapy. On the other hand, gold silica nanoparticles, nanoshells, nanorods, nanocages, and nanotubes were especially studied as photothermal agents under radiofrequency or magnetic field activation in non-invasive imaging and cancer therapy.[239] Regarding drug delivery, nanoparticles have been engineered as drug vehicles to bring drug directly at the tumor site, to reduce toxic side effects of antineoplastic agents, and to enhance combinatorial drug delivery. Among all reported studies we highlighted the most promising ones. Recent studies focused on new strategies based on a combination therapy through a co-administration of multiple drugs using a single treatment. For example, this approach was carried out by Murugan *et al*.[240] to describe nanocarrier mediated inhibitory effects of topotecan and quercetin on BC cells like a new targeted therapeutic strategy to treat cancer. These revolutionary nanocarries have shown an excellent intracellular release of loaded drugs with important molecularl-induced modifications leading to structural charges in endoplasmatic reticulum, nucleus and mitochondria in tumor cells.[240]

Nanotechnology can offer potential nanomaterials for creating new methods for detection, targeting and killing BC at different stages. Several authors reported the problematic use of many nanomaterials because of their non-specific toxic effects in *in vivo* animal models. One of the major advantages of using nanoparticles are based on the possibility to modify their characteristics to face physical and biological barriers after injection. However, the analysis of the recent publications disclosed that the delivery efficiency has not advanced during the last ten years.

Regarding innovative approaches able to accelerate the nanotool integration into the clinic, we would like to mention single cell techniques and in particular single cell mass cytometry. We recently described how this approach could reveal the effect of graphene and nanomaterials in general on immune cells.[241] Being aware that single cell mass cytometry can be useful in the context of BC, as proven recently by the group of Bodenmiller, [242], we believe it will be of interest to apply this approach on nanotools to validate their effect on BC treatment.

In conclusion, despite the numerous studies found in the literature, only a few nanomaterials or nano-compounds will move on from the pre-clinical phase and will be selected for clinical trials. Indeed, the research on biocompatibility are still at the early stage. Given the great interest reported in recent years, graphene could be one of the promising nanomaterial to fight BC. Moreover, at present, the possibility to control the nanoparticles transport and the real delivery efficiency in the body for cancer treatment remains the real challenge for nanotechnology-based tools against BC.

Conflicts of interest

There are no conflicts to declare.

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Figure captions

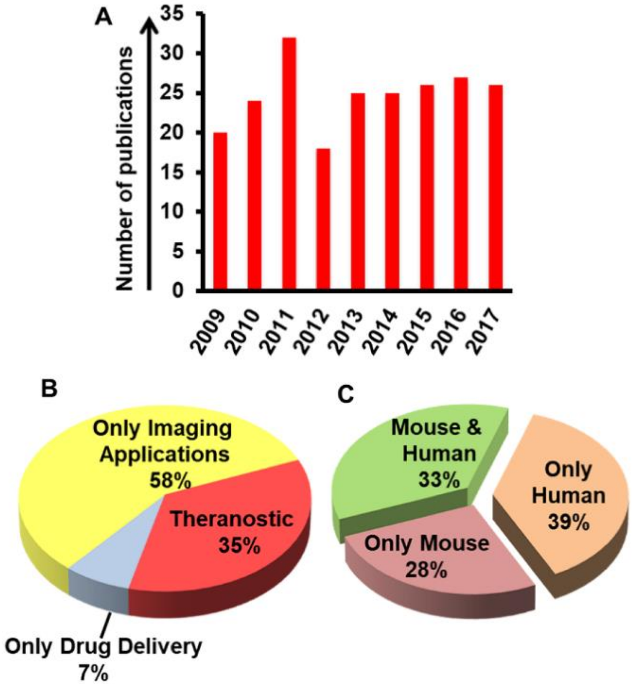


Fig. 1. Status of applications used on BC studies. A) Analysis of publications in the last 9 years (2009 to 2017). B) Relative percentages of publications for imaging, theranostic and drug delivery applications. C) Species examined in each publications (human, mouse and combination of human and mouse).

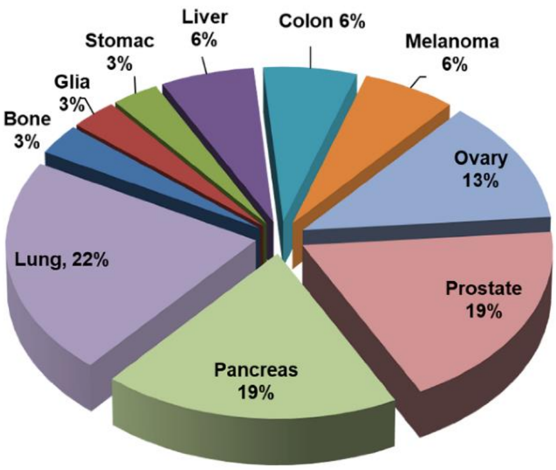


Fig. 2. Percentage of publications focusing on other types of cancer together with BC.

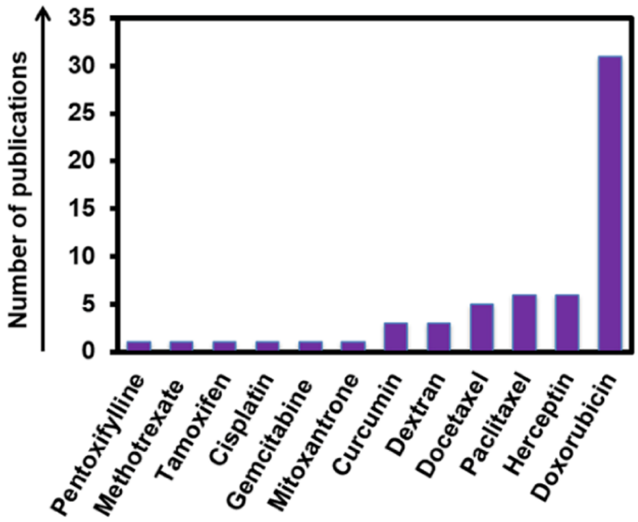


Fig. 3. Conjugated drugs to nanomaterials. Number publications in the last 9 years based on the type of drugs conjugated to nanomaterials and nanoparticles to fight BC.

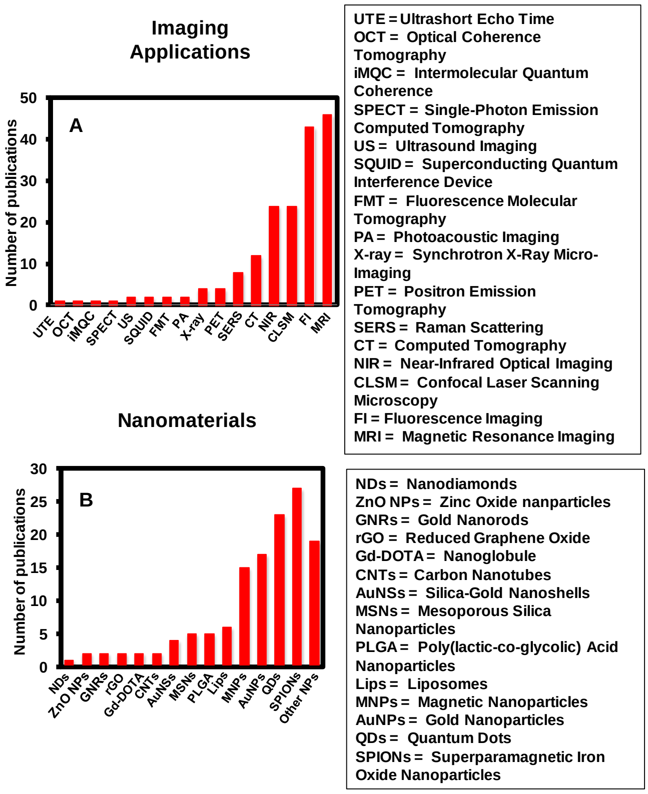


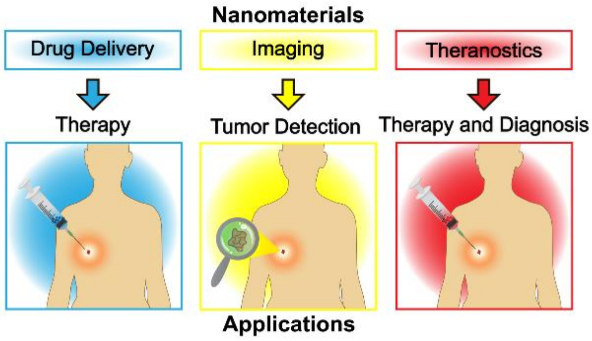
Fig. 4. Overview on different types of techniques and nanomaterials for imaging. A) Analysis of the number of publications based on the different kind of Imaging Applications for BC. B) Types of nanomaterials used for imaging.

THERANOSTIC MATERIAL	Abbreviation
Magnetic Nanoparticles	MNPs
Calcium Phosphosilicate Composite Nanoparticles	CPSNPs
Liposomes	Lips
Gold Nanoparticles	AuNPs
Gold Nanorods	GNRs
Gold Nanoshells	AuNSs
Carbon Nanotubes	CNTs
Hydrotropic oligomer-conjugated nanoparticles	HO-CNPs
Nanoparticles	NPs
Mesoporous Silica Nanoparticles	MSNs
Quantum Dots	QDs
Copper(II) sulfide nanoparticles	CuS NPs
Superparamagnetic Iron Oxide Nanoparticles	SPIONs
Tungsten oxide Nanoparticles	WO3-x
Thiol-functionalized hyaluronic acid	HS-HA
Mesoporous Magnetic Gold “nanoclusters”	MMGNCs
Heparinefolic acid nanoparticles	HFNPs
Reduced Graphene Oxide	rGO
Carbon Nano-Onions	CNOs

Fig. 5. List and acronyms of nanomaterials used as theranostic in the treatment of BC.

Graphical Abstract

Different nanomaterials have been developed to fight against breast cancer.



How can nanotechnology help the fight against breast cancer?

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ELECTRONIC SUPPLEMENTARY INFORMATION

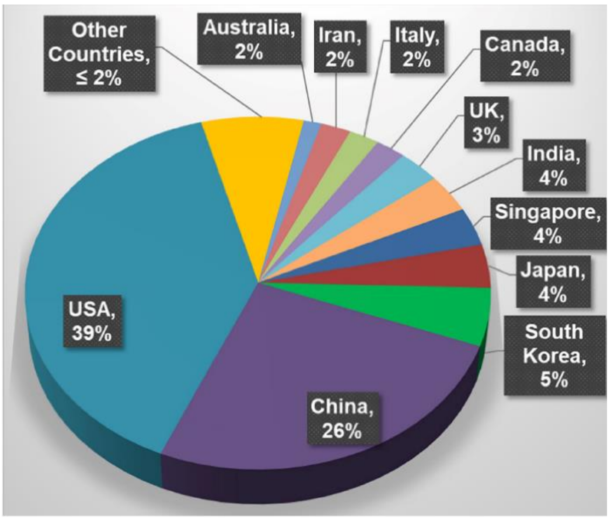
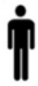
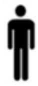
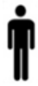
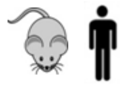
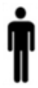
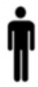
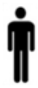
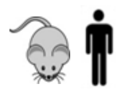


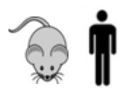
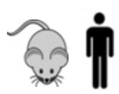
Fig. S1. Percentage of publications carried out on nanomaterials fight against BC per Countries. The piece of the cake in yellow, reported the studies in a percentage of <2 % conducted in other countries such as: New Zealand, Greece, Brazil, Taiwan, Malaysia, Riyadh-Saudi Arabia, The Netherlands, Israel, Germany, France, Georgia, Poland.

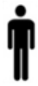
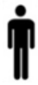
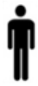
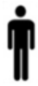
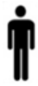
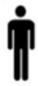
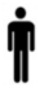
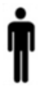
Table S1: Drug delivery

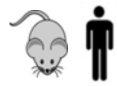
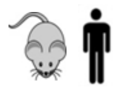
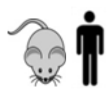
Material	Drug	Imaging	Model	Cell type	Ref.*
Poly(lactic-co-lycolic) Acid Nanoparticles	Dextran (T-40)	Fluorescence imaging	In vivo / In vitro (MCF-7 cells)		[42]
Poly(lactic-co-glycolic) Acid Nanoparticles	Doxorubicin	CLSM	In vivo / In vitro (C127I cells)		[22]
Paclitaxel Nanoparticles	Paclitaxel	Fluorescence imaging	In vivo (MCF-7 cells)		[36]
Paclitaxel Nanoparticles	Paclitaxel	CLSM, NIR	In vivo / Intro (MCF-7 cells)		[35]
FeCo/Graphitic Carbon Shell Nanocrystals	Doxorubicin	MRI, NIR	In vitro (MCF-7 cells)		[23]
Superparamagnetic Iron Oxide Nanoparticles	Doxorubicin	CLSM	In vitro (MCF7 cells)		[24]
Liposomes	Doxorubicin	CLSM, Fluorescence imaging	In vivo / In vitro / Ex vivo (MDA-MB-231 cells)		[71]
Mesoporous Silica Nanoparticles	Paclitaxel	CLSM	In vitro (MDA-MB-231, MDA-MB-468)		[38]
Poly(lactic-co-glycolic) Acid Nanoparticles	Curcumin	CLSM	In vitro (MDA-MB-231 cells)		[39]
Mesoporous Silica Nanoparticles	Antibody (Her2-neu Herceptin)	MRI, CLSM	In vitro (SKBR-3 cells)		[28]
DNA Origami	Doxorubicin	Fluorescence imaging	In vivo / Ex vivo (MDA-MB-231 cells)		[21]
Gold Nanorods and Gold Nanoparticles	Docetaxel	CLSM	In vitro (MCF7 and B16F10 cells)		[44]
PLGA-TPGS Nnanoparticles	Docetaxel	CLSM	In vivo / In vitro (MCF-7/TXT cells)		[45]
Iron-Oxide Nanoparticles	Peptides	CLSM	In vivo (MCF10CA1a model)		[8]
Solid Polymer-Lipid Nanoparticles	Ibuprofen, Naproxen	Fluorescence imaging	In vitro / In vivo / Ex vivo (EMT6, MDA-MB-231, DU145 cells)		[9]

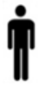
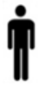
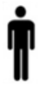
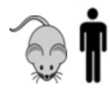
* The reference numbers in the table refer to those in the main text.

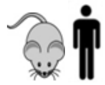
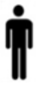
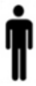
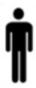
Table S2: Imaging applications

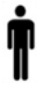
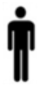
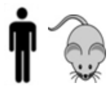
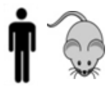
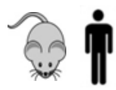
Material	Conjugated molecules	Imaging	Model	Cell type	Ref.*
Poly(lactic-co-glycolic) Acid Nanoparticles	Rhodamine-6G	Fluorescence imaging	In vitro (MDA-MB-231 cells)		[80]
Quantum Dots	Poly(lactide)-Vitamin E TPGS	CLSM	In vitro (MCF-7 cells)		[120]
Superparamagnetic Iron Oxide Nanoparticles	NIR Dye (Cy5.5), Peptides	MRI, NIR	In vivo / In vitro / Ex vivo (BT-20 cells)		[79]
Liposomes	Iodine	CT	In vivo / In vitro (R3230AC cells)		[144]
Gold Nanoparticles	Sodium Dodecyl Sulphate, Polyethylene Glycol	CLSM	In vitro (Hs578T cells)		[121]
Hollow Gold Nanospheres	Dihydrolipoic Acid, Raman Reporter, Anti-rabbit IgG	SERS, Fluorescence imaging	In vitro (MCF-7 cells)		[81]
Superparamagnetic Iron Oxide Nanoparticles	Luteinizing Hormone Releasing Hormone	iMQC	In vivo / In vitrio (MDA-MB-435, PC-3 cells)		[164]
Magnetic Nanoparticles and Golden Carbon Nanotubes	Amino-Terminal Fragment of the Urokinase Plasminogen Activator, Polyethylene Glycol, Folic Acid	Fluorescence imaging	In vivo / In vitro (MDA-MB-231 cells)		[82]
Magnetic Nanoparticles	Urokinase Plasminogen Activator, NIR Dye (Cy5.5)	MRI, NIR, Fluorescence imaging	In vivo / In vitro (4T1, T47D cells)		[83]
Quantum Dots	Antibody (AVE-1642), Small molecule, Fluorophore (Alexa 680)	CLSM, Fuorescence imaging	In vivo / In vitro (MCF-7 cells)		[122]
Gold Nanorods	14-Amino Acid Peptide Bombesin	Fluorescence imaging	In vitro (PC-3, T-47D cells)		[84]

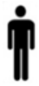
Quantum Dots	Antibodes (anti-CD44v6, anti-CD24)	Fluorescence imaging	In vitro (Tumor Tissue)		[85]
Gold Nanoparticles	Bovine Serum Albumin	Fluorescence imaging	In vitro (MCF-7 cells)		[5]
Mesoporous Silica Nanoparticles	Antibody (anti-EGFR)	Fluorescence imaging	In vitro (MCF-7 cells)		[86]
Gold Nanoparticles	Antibody (anti-EGFR)	Fluorescence imaging	In vitro (A431, 270-GBM, H2224, MDAMB-453 cells)		[87]
Silica-Gold Nanoshells	Polyethylene Glycol, P-mercaptoaniline	SERS	In vitro (MCF-7 cells)		[154]
Silica-Gold Nanoshells	Polyethylene Glycol, Antibody (anti-HER2)	NIR, MRI, Fluorescence imaging	In vivo / In vitro (BT474AZ, MDAMB231 cells)		[56]
Quantum Dots	Prtein A, Antibody (anti-CXCR4, anti-HER2), Polyethylene Glycol	Fluorescence imaging	In vitro (KPL-4 cells)		[88]
Silica-Gold Nanoshells	–	OCT	Ex vivo (Tumor Tissue)		[165]
Gold-Gold Sulfide Nanoparticles	Antibodies (anti-HER2, anti-IgG)	CLSM	In vitro (SK-BR-3 cells)		[123]
Superparamagnetic Iron Oxide Nanoparticles	Poly2-hydroxyethyl Aspartamide, Antibody (HER2/neu)	MRI	In vitro (H520, SKBR-3 cells)		[57]
Magnetic Nanoparticles	Oleic Acid, Polyethylene glycol, Antibodies (IgG, anti-HER-2)	MRI, CLSM	In vitro (MCF-7 cells)		[58]
Quantum Dots	Polystyrene Polymer	Fluorescence imaging	In vitro (MCF-7 cells)		[89]
Quantum Dots	Antibody (anti-PAR1)	Fluorescence imaging	In vivo / In vitro (KPL-4 cells)		[90]

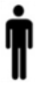
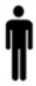
Superparamagnetic Iron Oxide Nanoparticles	Polylactic acid, D-α-Tocopherol Polyethylene glycol 1000 Succinate	MRI	In vivo / In vitro (MCF-7 cells)		[59]
Polylactic-co-glycolic Acid Nanoparticles	Nanoparticles, Gadolinium-Diethylenetriamine Penta-Acetic Acid	MRI	In vivo / In vitro (MCF-7 cells)		[60]
Quantum Dots	Polyethylene Glycol Phosphatidylethanolamine, Antibody (anti-nucleosome 2C5)	NIR	In vivo / Ex vivo (4T1, B16F10 cells)		[135]
Superparamagnetic Iron Oxide Nanoparticles	–	MRI	In vivo (Tumor Tissue)		[54]
Superparamagnetic Iron Oxide Nanoparticles	–	MRI, CT	In vivo (Tumor Tissue)		[145]
Perfluorocarbon Nanoparticles	NIR Peptides (Cypate-cRGDfK Cypate-C18)	NIR	In vivo / Ex vivo (4T1 cells)		[136]
Poly(n-butyl cyanoacrylate) Nanocapsules	Cyanine (IR-768)	CLSM	In vitro (MCF-7 cells)		[124]
Superparamagnetic Iron Oxide Nanoparticles	Free Folic Acid	MRI	In vivo / In vitro (MDA-MB-231 cells)		[61]
Silica-Gold Nanoshells	Polyethylene Glycol, Antibodies (anti-HER2/neu, anti-IgG)	NIR	In vitro (SK-BR-3, HCC1419, JIMT-1 cells)		[137]
Nanoglobules	Peptide (CLT1)	MRI	In vivo / In vitro (MDA-MB-231 cells)		[62]
Superparamagnetic Iron Oxide Nanoparticles	D-a-Tocopheryl-co-polyethylene glycol-1000 succinate, Copolymer (Pluronic®F127)	MRI	In vivo / In vitro (MCF-7 cells)		[63]
Gold Nanoparticles	Polyethylene Glycol, Antibody (HER81)	SEM	In vitro (SK-BR-3 cells)		[173]

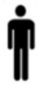
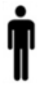
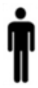
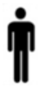
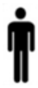
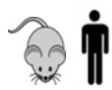
Liposomes	Iodine	CT	In vivo / In vitro (4T1 cells)		[146]
Magnetic Nanoparticles	Fluorophores (Feridex, Dextranase)	MRI, CLSM	In vivo / In vitro (MCF-7 cells)		[125]
Magnetic Nanoparticles	Polyethylenimine, Polyethylene Glycol, siRNA	CLSM	In vitro (MCF-7, TC2 cells)		[126]
Upconversion Nanoparticles	Polyethyleneglycol, Chlorin e6	NIR, CLSM	In vivo / In vitro (4T1 cells)		[127]
Mesoporous Silica Nanoparticles	NIR Dye	NIR	In vivo (4T1, luc-D3H2LN MDA-MB-23 cells)		[138]
Magnetic Nanoparticles	5-Aminolevulinic Acid, Indocyanine Green Dye	CT, NIR	In vivo (Tumor Tissue)		[139]
Quantum Dots	Antibodies (anti-HER2, anti-collagen IV)	Fluorescence imaging	In vitro (Tumor Tissue)		[91]
Gold Nanoparticles	Polyethylene Glycol, Antibodies (anti-Her2)	CT	In vivo / In vitro (BT-474, MCF7 cells)		[147]
Superparamagnetic Iron Oxide Nanoparticles	–	MRI	In vivo (Breast tissue)		[13]
Quantum Dots	Tetraethyl Orthosilicate, Antibody (anti-EGFR)	Fluorescence imaging	In vitro (MDA-MB-435S, SMMC-7721 cells)		[92]
Liposomes	Thioated Oligonucleotide Aptamer, E-selectin, Polyethylene Glycol	Fluorescence imaging	In vivo / In vitro (MDA-MB-435S, SMMC-7721 cells)		[93]
Polyβ-L-malic Acid Platform	Antibody (anti-HER2/neu), NIR Dye (Alexa Fluor 680), Polyethylene Glycol	CLSM	In vivo / In vitro (BT-474, SKBR-3, MDA-MB-231, MDA-MB-435, MDAMB-468 cells)		[128]

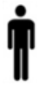
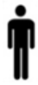
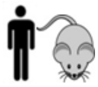
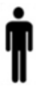
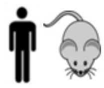
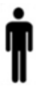
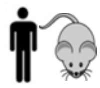
Quantum Dots, Superparamagnetic Iron Oxide Nanoparticles	Polylactic Acid-d-a-Tocopheryl Polyethylene Glycol 1000 Succinate Nanoparticles	MRI, CLSM, Fluorescence imaging	In vivo / In vitro (MCF-7 cells)		[64]
Superparamagnetic Iron Oxide Nanoparticles	Quantum Dots, Superparamagnetic Iron Oxide Nanoparticles, Antibody (anti Her2)	SQUID, Fluorescence imaging	In vivo / In vitro (MCF-7, MDA-MB-231, BT-474 cells)		[94]
Superparamagnetic Iron Oxide Nanoparticles	–	MRI, CT	In vivo (Breast tissue)		[148]
Photoswitchable Nanoparticles	Antibody (anti-Her2)	NIR, Fluorescence imaging	In vitro (SK-BR-3 cells)		[96]
Quantum Dots	Polyethyleneglycol, Fatty Ester Matrix	Fluorescence imaging	In vivo (MDA435 cells)		[95]
Magnetic Nanocluster	Pyrenyl Hyalurone	MRI	In vivo / In vitro (MDA-MB-231 cells)		[65]
Nanoglobule	–	MRI	In vivo (MDA-MB-231 cells)		[66]
Mesoporous Silica Nanoparticles	NIR Dye (MDT)	NIR	In vivo (4T1 cells)		[140]
Superparamagnetic Iron Oxide Nanoparticles	Chitosan, Polyethylene Glycol, Antibody (Neu)	MRI, CLSM	In vivo / In vitro / Ex vivo (MMC cells)		[67]
Superparamagnetic Iron Oxide Nanoparticles	Dimercaptosuccinic Acid, 2-Deoxy-d-Glucose	MRI	In vitro (MDA-MB-231 cells)		[68]
Magnetic Nanoparticles	Gold, Lanthanidedoped Rare-Earth Nanocrystals, Polyethylene Glycol	MRI	In vivo (4T1 cells)		[69]

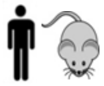
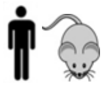
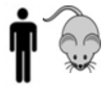
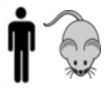
Multiwalled Carbon Nanotubes	Magnetite Nanoparticles, Polyethylene Glycol	CLSM	In vivo / In vitro (MCF7, MDA MB231 cells)		[129]
Magnetic Nanoparticles	Integrin (αvβ3), Amines (DTSSP)	MRI, FMT, CT	In vivo / Ex vivo (4T1 cells)		[70]
Poly(lactic-co-glycolic) Acid Nanoparticles	Indocyanine Green, Folic Acid	NIR, Fluorescence Imaging	In vivo / In vitro (MCF7 cells)		[97]
Poly(lactic-co-glycolic) Acid Nanoparticles	Magnetic Nanoparticles	MRI, US	In vivo / In vitro (VX2 cells)		[71]
Gold Nanoparticles	Peptides (p12, CRGDH)	CLSM	In vitro (MDA-MB-231, MCF-7 cells)		[130]
Quantum Dots	Antibody (Anti-GRP78 scFv)	Fluorescence imaging	In vitro (MDA-MB-231 cells)		[98]
Quantum Dots	Antibody (Anti-HER2)	NIR, MRI, Fluorescence imaging	In vivo / In vitro (KPL-4 cells)		[99]
Gold Nanoparticles	Antibody (CD24, CD44)	SERS	In vitro (MDA-MB-231 cells)		[155]
Gold Nanoparticles	Wheat-Germ Agglutinin, Polyethylene Glycol	NIR	In vivo / In vitro (BT549 cells)		[141]
Magnetic Nanoparticles	Antibody (Anti-HER2)	MRI, SQUID	In vivo / In vitro (MCF7 cells)		[153]
Magnetic Nanoparticles	Fluorophores (TRITC)	CLSM	In vivo / In vitro (MTGB cells)		[131]
Magnetic Nanoparticles	3-Aminopropyl triethoxysilane, Antibody (Anti-HER2)	MRI	In vivo / In vitro (MDA-MB-231, SKBR-3, MDA-MB-453, MCF7, 4T1 cells)		[72]

Superparamagnetic Iron Oxide Nnanoparticles, Liposomes	Polyethylene Glycol, Rhodamine-DHPE	MRI, Fluorescence imaging	In vivo / In vitro (MDA-MB-453, MCF-7 cells)		[100]
Quantum Dots	Magnetic Beads, Nucleolin Aptamer AS1411	Fluorescence imaging	In vitro (MCF-7 cells)		[101]
Magnetic Nanoparticles	Dopamine-Polyethylene Glycol	Fluorescence imaging	In vitro (MCF-7 cells)		[102]
Graphene Oxide	Antibody (Anti-HER2), ^{111}In-benzyl-diethylenetriamine-pentaacetic acid	SPECT	In vivo / In vitro (MDA-MB-231 cells)		[163]
Superparamagnetic Iron Oxide Nanoparticles	–	MRI	In vivo (4T1 cells)		[167]
Gold Nanoparticles	Dendrimers	MRI, CT	In vivo / In vitro (MCF7 cells)		[149]
Superparamagnetic Iron Oxide Nanoparticles	–	MRI	In vivo / In vitro (4T1 cells)		[168]
Magnetic Nanoparticles	MiRNA (Anti miR-10b)	MRI	In vivo / In vitro (MDAMB-231 cells)		[171]
Gold Nanoparticles	Thioglycolic acid, 6-Thioguanine, 2-Mercaptoethanol, 1-Propanthiol	X-Ray	In vitro (MDAMB-231 cells)		[160]
Mesoporous Silica Nanoparticle	^{64}Cu, Antibody (TRC105)	PET, NIR	In vivo / In vitro (4T1 cells)		[142]
Magnetic Nanoparticles	Polyethylene Glycol, Antibody (anti-EGFR)	MRI, CLSM, FMT	In vivo / In vitro (MDA-MB-231, MDA-MB-453 cells)		[73]

Gold Nanoparticles	Thiol-PEG, 3-Aminopropyl triethoxysilane	Fluorescence imaging	In vivo / In vitro (MDA-MB-231LM2 cells)		[103]
Superparamagnetic Iron Oxide Nanocomposites	Polyethylenimine, siRNA	MRI, CLSM	In vivo / In vitro / Ex vivo (MCF-7/ADR cells)		[74]
Quantum Dots	–	NIR, CLSM	In vitro (MCF-7/WT cells)		[132]
Superparamagnetic Iron Oxide Nanoparticles	Amino Terminal Fragment, Antibody (SvFcEGFR)	NIR, MRI, UTE	In vivo / In vitro (MiaPaCa-2, 4T1CFhR cells)		[166]
Superparamagnetic Iron Oxide Nanoparticles	Antibody (anti-ICAM1), Casein	MRI, Fluorescence imaging	In vivo / In vitro (MDA-MB-231, MCF7, MCF10A cells)		[104]
Mesoporous Silica Nanoparticles	Polyethyleneimine, Folic Acid, RNA interference (Notch-1 shRNA)	MRI, CLSM	In vitro (MDA-MB-231 cells)		[75]
Gold Nanoparticles	Bisphosphonate	CT, X-ray	In vitro / Ex vivo (Tumor Tissue)		[150]
Hyaluronic Acid Derived Nanoparticles	Aminopropyl-1-pyrenebutanamide, Aminopropyl-5β-cholanamide, Octadecylamine	Fluorescence imaging	In vivo / In vitro (MDA-MB-231 cells)		[105]
Zinc Oxide Nanoparticles	Antibody (^{64}Cu, TRC105)	Fluorescence imaging, PET	In vivo / Ex vivo (4T1 cells)		[106]
Superparamagnetic Iron Oxide Nanoparticles	Dextran, Bombesin	MRI	In vivo / In vitro (T47D)		[169]
Quantum Dots	Recombinant Protein (GST-EGFP-GB1), Antibody	Fluorescence imaging, NIR	In vivo / In vitro (T47D)		[107]

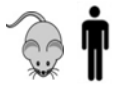
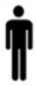
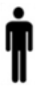
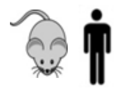
Quantum Dots	Antibodies (QD-655, QD-655)	Fluorescence imaging	In vitro / Ex vivo (Tumor Tissue)		[108]
Quantum Dots	Antibodies (QD-655, QD-655, anti-Ki67 rabbit)	Fluorescence imaging	In vitro / Ex vivo (Tumor Tissue)		[109]
Conjugated Polymers	1,2-Distearoyl-sn-glycero-3-phosphoethanol-amine-N-[methoxy(polyethylen eglycol)-2000], Folate	CT	In vivo / In vitro (MCF-7 cells)		[151]
Gold Nanoparticles	–	CT, X-ray	In vivo (WT and PyMT mice)		[152]
Quantum Dots	Antibody (anti-PAR1-QDs)	Fluorescence imaging	In vitro / Ex Vivo (KPL-4)		[110]
Polymer Nanoparticles	–	MRI	In vivo (Breast Tissue)		[55]
Superparamagnetic Iron Oxide Nanoparticles	Liposomes	MRI	In vivo / In vitro (4T1, MDA-MB-231 cells)		[76]
Poloxamer Blend Nanoparticles	Poloxamer 180, IR820	Fluorescence images	In vitro (MCF-7 cells)		[111]
Enzymatically Activated Fluorescent Nanoprobes	Fluorescent molecule (AF750)	Fluorescence images, NIR	In vitro (MDA-MB-231 cells)		[112]
Gold Nanoparticles	Integrin ($\alpha_v\beta_3$)	Fluorescence images, CT	In vitro / Ex vivo (4T1-GFP-luc)		[113]
Superparamagnetic Iron Oxide Nanoparticles	Dimercaptosuccinic Acid, 2-Deoxy-D-glucose	MRI	In vivo / In vitro (MCF-7 and MDA-MB-231 cells)		[77]

Layered Double Hydroxide	Isotopes	PET	In vivo (4T1 cells)		[162]
Nanodiamonds	Polyethylene glycol, Antibody (anti-HER2)	PAI	In vivo / In vitro (4T1 cells)		[179]
Quantum Dots	Amphiphilic poly(maleic anhydride-alt-1-octadecene) Polymer	Fluorescence images	In vitro (SKBR3 cells)		[114]
Nanoparticles	Receptor-targeted surface-enhanced Raman scattering	SERS	In vitro (SKBR3 cells)		[156]
Graphene Oxide	Antibody (^{64}Cu-NOTA-GO-FSHR-mAb)	PET, Fluorescence images	In vitro / In vivo (MDA-MB-231 cells)		[236]
Quantum Dots	Antibody (^{64}Cu-NOTA-GO-FSHR-mAb)	MRI, Fluorescence images	In vitro / In vivo (MDA-MB-231 cells)		[116]
Gold Nanorods, Superparamagnetic Iron Oxide Nanoparticles	Polyethylene Glycol, Cystamine (anti-EGFR)	MRI, Fluorescence images	In vitro (MCF7-231 cells)		[78]
SERS Nanoparticles	Antibodies (mAb anti-EGFR, anti-HER2, anti-CD44 / CD24)	SERS	In vivo / Ex vivo (A431 cells)		[157]
Silicon Nanoparticles	–	SERS	In vitro (MCF-7 cells)		[158]
Luminomagnetic Nanorods	–	Fluorescence images	In vitro (T47D, MDA-MB-231 cells)		[117]
Superparamagnetic Iron Oxide Nanoparticles	D/L-Lactide/Glycolide Copolymer	Fluorescence images	In vitro / In vivo (CT26, 4T1, LLC, B16F10 cells)		[118]

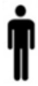
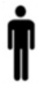
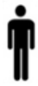
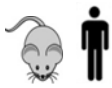
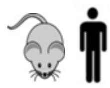
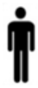
Quantum Dots	Metal-free/cadmium-free (bio CFQD®)	CLSM	In vitro / Ex vivo (MCF-7 cells)		[133]
Polyamidoamine-based Silica Nanoparticles	Antibody (anti-HER2)	NIR	In vitro / In vivo (SK-BR3, MDA-MB-231 cells)		[143]
Magnetic Nanoparticles	–	CLSM	In vitro (MDA-MB-231 cells)		[134]
Magnetic Nanowires	Antibody	FI	In vitro / Ex vivo (MCF-7, MDA-MB-231 cells)		[119]
Gold Nanostars	Antibody	SERS	In vitro / In vivo (MDA-MB-231, MDA231-LM2 cells)		[175]
Zinc Oxide Nanoparticles	Carbon Nanoparticles	CLSM	In vitro (MCF-7 cells)		[174]
Liposomes	Ammonium bicarbonate	PAI	In vitro / In vivo (MDA-MB-231 cells)		[177]
Poly(lactic-co-glycolic) Acid Nanoparticles	MMP2	MRI, NIR	In vitro / In vivo (MDA-MB-231 cells)		[176]
SERS Nanoparticles	–	SERS	In vitro (SKBR3, MDA-MB-231 cells)		[159]
Quantum Dots	–	FI	Ex vivo (Tumor tisue)		[172]
Gold Nanoparticles	HEPES, Bombesin, PEG	X-ray	In vitro / In vivo (T47D cells)		[161]
Superparamagnetic Iron Oxide Nanoparticles	Fluorescein-5-maleimide-labeled DARPin G3	MRI	In vitro / In vivo (SKBR-3, MDA-MB-231, HL-7702 cells)		[170]

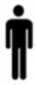
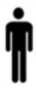
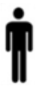
* The reference numbers in the table refer to those in the main text.

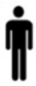
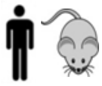
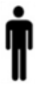
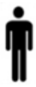
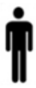
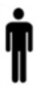
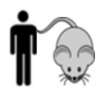
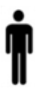
Table S3: Theranostic applications

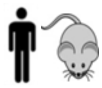
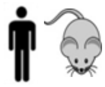
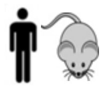
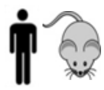
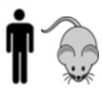
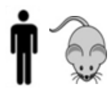
Material	Conjugated molecules	Theranostic applications	Model	Cell type	Ref.*
Magnetic Nanoparticles	Oleic Acid, Copolymers (Pluronic®F68, F108, L64, Tetronic®T904, T908)	Tumor Detection	In vivo / In vitro (MCF-7 cells)		[182]
Superparamagnetic Iron Oxide Nanoparticles	Dextran (T-40), Antibody (Herceptin)	Tumor Detection, Drug Delivery	In vivo / In vitro (MCF-7, BT-474, SKBR-3, MDA-MB-231 cells)		[33]
Gold Nanorods	Iron Nanoaprticles, Poly ethylene Glycol, Antibody (Herceptin)	Tumor Detection, Drug Delivery	In vitro (MCF-7, SK-BR-3 cells		[32]
Gold Nanorods	Antibody (Herceptin), Polyethylene Glycol	Tumor Detection, Delivery	In vivo / In vitro / Ex vivo (MCF-7, BT-474 and SKBR-3 cells)		[31]
Calcium Phosphosilicate Composite Nanoparticles	Antibody (anti-CD71), Avidin	Tumor Detection, Drug Delivery	In vivo / In vitro (BxPC-3, MDA-MB-231 cells)		[214]
Single-Walled Carbon Nanotubes	Copolymers (Pluronic® F127)	Thermal Therapy	In vitro (Tumor Tissue)		[210]
Magnetic Nanoparticles	Oleic Acid, NIR dye (5700, 5177, 2826, 6825, 5491), Copolymers (Pluronic ®F127)	Tumor Detection	In vivo / Ex vivo (MCF-7 cells)		[183]
Magnetic Nanoparticles	Dextran (T-40), NIR Dye (Cy5.5), Peptides (EPPT), siRNA	Drug Delivery, Cancer Therapy	In vivo / In vitro / Ex vivo (BT-20, CAPAN-2, LS-174T cells)		[43]
Silica-Gold Nanoshells	Polyethylene Glycol, Antibody (anti-HER2)	Photothermal Therapy, Gene Therapy	In vivo / In vitro (SKBR3, MDAMB231, BT474AZ cells)		[180]
Silica-Gold Nanoshells	Polyethylene glycol, 3,3′-diethylthia-tricarbocyanine iodide	Photodynamic Therapy	In vitro (BT549 cells)		[190]

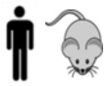
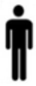
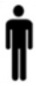
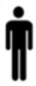
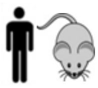
Magnetic Nanoparticles	Human Serum Albumin, Doxorubicin	Tumor Detection, Drug Delivery	In vivo / In vitro / Ex vivo (4T1 cells)		[184]
Thiol-functionalized Hyaluronic Acid	Allyloxy 12Cucurbit[6]uril, Fluorescein Isothiocyanate	Drug Delivery, Tissue Engineering	In vitro (B16F1, FPRL1/MCF-7 cells)		[223]
Magnetic Nanoparticles	β-Cyclodextrin, Copolymer (Pluronic®F127), Curcumin	Drug Delivery, Cancer Therapy	In vitro (MDA-MB-231, MCF-7, A2780CP, PC3 cells)		[41]
Magnetic Nanoparticles	Antibody (anti-HER2)	Cancer Therapy	In vivo / Ex vivo (MCF-7 cells)		[186]
Gold Nanoparticles	Molecule (DOTA-^{64}Cu), Amine Polyethylene Glycol Thiol	Tumor Detection	In vivo (EMT-6 cells)		[195]
Liposomes	Docetaxel, D-α-Tocopheryl Acid Succinate, Quantum Dots	Tumor Detection, Drug Delivery	In vitro (MCF-7 cells)		[44]
Magnetic Nanoparticles	Copolymers (Pluronic®F68), Curcumin	Drug Delivery	In vitro (MDA-MB-231 cells)		[40]
Gold Nanoparticles	Polyethylene glycol	Phototermal Therapy, Tumor Detection	In vivo / In vitro (MDA-MB-435 cells)		[196]
Calcium Phosphosilicate Nanoparticles	Polyethylene glycol, Indocyanine green	Photodynamic Therapy	In vivo (410.4, MDA-MB-231, Panc-02, BxPC-3-GFP, SAOS-2-LM7 cells)		[215]
Reduced Graphene Oxide	Antibody (Anti-CD105), ^{64}Cu-NOTA-TRC105	Phototermal Therapy	In vivo / in vitro / Ex vivo (4T1, MCF-7 cells)		[236]
Heparine/Folic acid Nanoparticles	IR-780 iodide	Phototermal Therapy	In vivo / In vitro (MCF-7)		[224]

PMAA-PS 80-g-St-DTPA polymer	Gadolinium, Doxorubicin	Drug Delivery	In vivo / In vitro (EMT6/WT cells)		[226]
Multiwalled Carbon Nanotubes	Alexa-fluor (AF488/647), Radionucleide (Technitium-99m), Folic Acid, Methotrexate	Tumor Detection, Drug Delivery	In vivo / In vitro (MCF-7, A549 cells)		[48]
Silica-Gold Nanoshells	Protoporphyrin IX, Peptide (TAT), 3,3'-diethylthia-dicarbocyanine iodide	Photodynamic Therapy	In vitro (BT-549 cells)		[191]
Magnetic Nanoparticles	Polyethylene glycol, Folic Acid, Tamoxifen	Tumor Detection, Drug Delivery	In vitro (MCF-7 cells)		[47]
Magnetic Nanoparticles	Acid (PHBA)-b-P(OEGA), Doxorubicin	Drug delivery	In vitro (MCF-7, H1299 cells)		[188]
Gold Nanorods	Polyethylene Glycol, Chlorin e6	Photothermal Therapy	In vivo / In vitro (MDA-MB-453 cells)		[206]
Mesoporous Silica Nanoparticles	Polyethylene glycol, Antibody (TRC105), Doxorubicin	Drug delivery, Tumor Detection	In vivo / In vitro / Ex vivo (4T1, MCF7 cells)		[201]
Hydrotropic Oligomer-Conjugated Nanoparticles	Glycol, Chitosan, Paclitaxel (PTX)	Cancer Therapy, Drug Delivery	In vivo / In vitro / Ex vivo (MDAMB-231 cells)		[227]
Silica-Gold Nanoshells	–	Photothermal Therapy, Ultrasonograp hy	In vivo / In vitro (BT474 cells)		[192]
Magnetic Nanoparticles	NIR Dye (830-ATF), Doxorubicin	Tumor Detection, Drug Delivery	In vivo / In vitro (MDA-MB-231, MIA PaCa-2 cells)		[185]
Gold Nanorods	Fluorescein Isothiocyanate, Fluorophore (TAMRA), siRNA	Gene Therapy	In vitro (MCF-7, SK-OV-3 cells)		[205]

N-(2-Hydroxypropyl) methacrylamide Copolymer	Paclitaxel, NIR Dye (SQ-Cy5)	Tumor Detection, Drug Delivery	In vivo / In vitro (4T1 cells)		[37]
Gold Nanoparticles	SERS Molecules (MGITC, Rh6G, Cy5)	Tumor Detection	in vivo / In vitro (MDA-MB-231 cells)		[197]
Mesoporous Silica Nanoparticles	Fluorescein Isothiocyanate, Antibody (Herceptin+D8)	Drug Delivery, Tumor Detection	In vitro (MDA-MB-231, SK-BR-3 cells)		[30]
Liposomes	Magnetic Nanoparticles, Mitoxantrone	Tumor Detection, Drug Delivery	In vivo / In vitro (MCF-7, SK-OV-3 cells)		[46]
Poly(methacrylic acid)-polysorbate 80-grafted-starch	Gadolinium, HiLyte Fluor 750, FA dye, Doxorubicin	Tumor Detection, Drug Delivery	In vivo / In vitro / Ex vivo (MDA-MB-231 cells)		[225]
Copper(II) Sulfide Nanoparticles	Polyethylene Glycol	Photoacoustic Tomography, Tumor Detection	In vivo / In vitro (4T1 cells)		[218]
Mesoporous Magnetic Gold Nanoclusters	Doxorubicin, Pentoxifylline	Photothermal Therapy, Drug delivery	In vivo / In vitro (4T1, MCF-7 cells)		[49]
Tungsten Oxide Nanoparticles	Polyethylene Glycol	Photothermal Therapy	In vivo / In vitro (4T1 cells)		[219]
Quantum Dots	Mercaptoundecanoic Acid, Antibody (Anti-HER2)	Tumor Detection	In vitro (SK-BR-3, MCF-7 cells)		[217]
Carbon Nano-Onions	Boron Dipyromethene	–	In vitro (MCF7 cells)		[238]
Singlewalled Carbon Nanotubes	Endoglin/CD105, Doxorubicin	Drug Delivery, Tumor Detection	In vitro / In vivo (4T1 cells)		[211]

Theranostic Nanoparticles	Chlorin e6, Monomethoxy polyethylene glycol	Chemotherapy Tumor Detection	In vitro (MDA-MB-231 TNBC cells)		[230]
Gold Nanoparticles	5-Fluorouracil	Tumor Detection, Cancer Therapy	In vitro / In vivo (MDA-MB-231 cells)		[198]
Star polymers	Doxorubicin, Gadolinium	Drug Delivery	In vitro (MCF7 cells)		[231]
Gold Nanorods	Tetraethylortho silicate, G70Cetyltrimethylam monium bromide	Photothermal Therapy	In vitro (MDA-MB-231 cells)		[207]
Magnetic Nanoparticles	Tetraethylortho-silicate, N-(2-aminoethyl)-3-aminopropyltrimetho-xysilane, Polyethylenimine, Small hairpin RNA	Gene Delivery	In vitro (MCF7 cells)		[189]
Polymeric Theranostic Nanoparticles	Docetaxel	Chemotherapy Drug Delivery	In vivo / In vitro (MDA-MB-231 cells)		[226]
Singlewalled Carbon Nanotubes	Doxorubicin, Hyaluronic acid, Gadolinium	Photothermal Therapy, Tumor targeting	In vitro / In vivo (MCF-7)		[212]
Quantum Dots	Chitosan, Folic acid	Tumor imaging, Drug Delivery	In vitro (MDA-MB-231, MCF-7 cells)		[241]
Liposomes	Doxorubicin	Tumor imaging, Drug Delivery	In vivo / In vitro / Ex vivo (MDA-MB-468, SKBR3 cells)		[208]
Gold Nanoparticles	Doxorubicin	Drug Delivery, Cancer Therapy	In vitro (MCF7 cells)		[199]
Gold Nanoparticles	Antibody(anti-HER2), Gadolinium	Tumor Detection, Cancer Therapy	In vitro (A549, SKBR-3 cells)		[29]

Nanocarriers	Paclitaxel	Drug Delivery, Cancer Therapy	In vitro (MCF-7/ADR cells)		[34]
Nanoreporters	Doxorubicin	Drug Delivery, Cancer Therapy	In vivo / Ex vivo		[233]
Gold Nanoroads	Cisplatin, Folic acid	Tumor Detection, Cancer Therapy	In vitro / In vivo / Ex vivo (4T1 cells)		[203]
Gold Nanoparticles	Doxorubicin, Gadolinium	Drug Delivery, Photothermal Therapy	In Vivo (Tumor models)		[18]
Porous Silicon Nanoparticles	–	Tumor Detection, Cancer Therapy	In vitro (MCF7 cells)		[202]
Gold Nanoparticles	Doxorubicin	Cancer Detection, Photothermal Therapy	In vitro / In vivo (MCF7 cells)		[200]
Singlewalled Carbon Nanotubes	Polyethylene Glycol, NIR Dye (Cy5.5)	Cancer Detection, Photothermal Therapy	In vitro / In vivo (MCF7 cells)		[213]
Gold Nanoparticles	Doxorubicin, Folic acid, BSA	Chemo-photothermal Synergistic Therapy	In vitro / In vivo (MCF7 cells)		[27]
Superparamagnetic Iron Oxide Nanoparticles	Hyaluronan	Cancer Detection, Photothermal Therapy	In vitro / In vivo (MDA-MB-231 cells)		[181]
Superparamagnetic Iron Oxide Nanoparticles	Folic Acid, Doxorubicin	Tumor Detection, Cancer Therapy	In vitro / In vivo (MCF7 cells)		[26]
Theranostic polymeric Nanoparticles	Docetaxel	Tumor Detection, Cancer Therapy	In vitro (MCF7, SKOV-3 cells)		[51]
Liposomes	Doxorubicin, Cisplatin, Gemcitabine	Tumor Detection, Cancer Therapy	In vitro / In vivo (MDA-MB-231, 4T1 cells)		[52]
Mesoporous Silica Nanoparticles	Doxorubicin	Tumor Detection, Cancer Therapy	In vitro / In vivo (4T1 cells)		[204]

Gd2O3@albumin Conjugating Photosensitizer	Chlorin e6	Cancer Detection, Photodynami Theraphy	In vivo / Ex vivo (4T1 cells)		[222]
Tumor-targeting Ultrasound-triggered Phase-transition Nanodroplets	Nucleic Acids	Tumor Detection, Cancer Therapy	In vitro / In vivo (SK-BR-3, HGC-27 cells)		[234]
Polylactic and Glycolic Acid Nanoparticles	L-Ferritin, Paclitaxel	Cancer Detection, Drug Delivery	In vitro (MCF7, MDA-MB-231 cells)		[228]
Gold Nanorods, Gold Nanospheres	Thiolated-hyaluronic acid	Cancer Detection, Photothermal Therapy	In vitro (MCF7 cells)		[193]
Carbon Nanoparticles Nanodroplets	Poly(lactic-co-glycolic acid)	Cancer Detection, Photothermal Therapy	In vitro / In vivo (MDA-MB-231 cells)	 (rabbit)	[220]
Prussian blue (PB)/manganese dioxide Hybrid Nanoparticles	–	Cancer Detection, Photothermal Therapy	In vitro / In vivo (MCF7 cells)		[221]
Magnetic Nanoparticles	Doxorubicin	Tumor Detection, Cancer Therapy	In vitro / In vivo (MDA-MB-231 cells)		[187]
Gold Nanospheres	Polyethylene Glycol	Cancer Detection, Photothermal Therapy	In vitro / In vivo (4T1 cells)		[194]
Peptide Aptamer Targeted Polymers	Doxorubicin	Cancer Detection, Drug Delivery	In vitro / In vivo (MDA-MA-231, MDA-MB-468		[229]
Liposomes	Doxorubicin	Tumor Detection, Cancer Therapy	In vitro / In vivo (4T1 cells)		[209]

* The reference numbers in the table refer to those in the main text.